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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,266	12/18/2003	Christian Auclair	1417-03	2270

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
11/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/740,266	AUCLAIR ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-47 and 50-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-47 and 50-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/17/2007 has been entered.

Claims 43-47 and 50-54 are currently pending and under consideration.

The declaration under 37 CFR 1.132 filed by Celine Bouquet is sufficient to overcome the rejection of claims 43-47 and 50 based upon the experiments conducted using mouse models. In particular, the showing that intratumoral injection of a recombinant adenovirus, e.g., AdZyxine, coding for the zyxine gene to a nude mouse inoculated with B16F10 murine melanoma cells inhibited tumor volumes by 79% and 73% as compared to controls (page 2, B16F10 tumor).

The declaration under 37 CFR 1.132 filed by Michel Jean Robert Perricaudet is sufficient to overcome the rejection of claims 43-47 and 50 for the reasons set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-47 and 50-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating B16F10 murine melanoma tumor cells in a patient comprising administering a therapeutically effective amount of a composition comprising a cDNA of a zyxin gene (see the declaration of Celine Bouquet), does not reasonably provide enablement for a method of treating hepatocarcinoma, mesenchymal tumors, neuroectodermal

cancer, Ewing's sarcoma and malignant hemopathies cancer in a patient comprising administering a therapeutically effective amount of a composition comprising cDNA of a zyxin gene, fragment thereof or a complementary sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in

the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims encompass a method of treating a particular tumor comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating or preventing hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies associated with chromosomal anomalies comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. Thus, the claims encompass method of treating in and/or all hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies in any patient including humans.

Quantity of experimentation

The quantity of experimentation in the areas of gene therapy for cancer and cancer prevention is extremely large given the unpredictability associated with treating a disease by a method of gene therapy, the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

Guidance in the specification and/or Presence of working examples

The specification teaches that pharmaceutical compositions for the treatment or prevention of tumoral pathology comprise an active agent which stabilizes the actin network of the cytoskeleton of a cell, wherein the agent includes, but is not limited to, a zyxin protein, a nucleic acid molecule comprising or constituted of the zyxin gene, a fragment thereof or their complementary sequence, or an antisense nucleic acid thereof, a cell or a set of cells over expressing the zyxin gene or a protein coded for a fragment thereof or an inhibitor of cofilin (page 9, paragraph 0036). The specification further teaches a pharmacological approach for the treatment of cancers by stabilization of the actin network, wherein NIH3T3 and EWS-Fli cells were contacted with dolastin 11 or jasplakinolide and the polymerization of actin was measured by fluorescence (page 30, paragraph 0108-0110). Moreover, the specification provides examples showing that expression of zyxin EWS-FLI cell lines reduce the tumorigenicity of the tumor cells in nude mice (paragraph 0099, Table 1). However, the specification appears to be silent on the in-vivo efficacy of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. The specification does not show any success in treating a disease by using a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. The specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. Specifically, the specification has not taught an appropriate tested dose for humans, the amount of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, and applicant has not enabled the pharmaceutical composition because it has not been shown that these polynucleotides are capable of functioning as to that which is being disclosed. Therefore, coupled with the unpredictability associated with using polynucleotides for the treatment or prevention of cancer, as underscored by the prior art below, the

criticality of providing workable examples in an unpredictable art, such as gene therapy and/or cancer therapy, is required for the practice of the instant invention.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize the unpredictability of treating a disease by a method of gene therapy. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2, *of record*). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1, *of record*). Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY, *of record*) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82). Also among the many factors that the art teaches

affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, "...the search for such combinations is a case of trial error for a given cell type" (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, *of record*, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142, *of record*) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411, *of record*) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. Similarly, Orkin et al (Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy, 1995) state that "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols" and further teach that significant problems remain in all basic aspects of gene therapy. Culver et al (TIG, 1994, 10:174-178) reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to

human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge " (p. 178). Further, Orkin et al reports major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host. (see page 1). In addition, the research community, as reported by Nature Biotechnology, 1997, 15:815, has responded to the issues raised in the Orkin Report drawn to vector based delivery systems, that is the critical steps of delivery of a gene to the right cell and the subsequent maintenance of gene expression, since it is now widely appreciated that the natural tropism of a virus, while advantageous to its own replication cycle is not always optimal for a gene delivery protocol and a number of laboratories have explored methods to redirect the targeting that has evolved to ensure viral infectivity in ways that may be more suitable to the aims of gene therapy and concludes that this return to first principles should help to continue to move gene therapy in the direction of its largest and most important ambitions (p. 815). Clearly, at the time the invention was made, gene therapy was an unpredictable art. This unpredictability was further clarified by the tragic setback, in 2002, in the most celebrated clinical trial drawn to the treatment of SCID in children wherein gene therapy led to cancer because of insertional mutagenesis (see Cheek [Nature, 2002, 420:116-118]) wherein the NIH urged all investigators conducting retroviral-mediated gene transfer in hematopoietic cells to discontinue enrollment and administration of the experimental agent until new data are available (see Attached Letter of January 14, 2003, Exhibit 1). Thus, the art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

With regards to preventing cancer, those of skill in the art recognize that reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence

of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Note: In order to expedite prosecution, the Examiner would like to address Applicants remarks to the previous rejection as they relate to the instant rejection. In response to the previous rejection, Applicants assert that the rejection takes the position that the specification is silent with respect to the in vivo efficacy aspect. However, Applicants assert that the specification nonetheless provides ample guidance to one skilled in the art to practice the subject matter particularly given the level of skill in the art, as acknowledged in the rejection (as being a PhD or MD). For example, Applicants submit a declaration by Celine Bouquet which contains the results of experiments conducted by the Declarant based on the teachings of Applicants original disclosure. In particular, Applicants submit that it can be seen that the tumor volume in Swiss nude mice was significantly inhibited by administration or treatment in multiple types of tumors. In addition, Applicants submit a

Declaration of Professor Michel Jean Robert Perricaudet whom is thoroughly skilled in the gene therapy art and points out that Ms. Bouquet was able to conduct experiments based on a reading of the specification, thereby confirming that Applicants specification fully enables the solicited claims.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner acknowledges and concedes that the Declaration by Celine Bouguet shows the in vivo efficacy of intratumoral injection of a recombinant adenovirus, e.g., AdZyxine, coding for the zyxine gene in Swiss nude mice inoculated with B16F10 murine melanoma cells. However, the Examiner recognizes that this showing in a mouse model using one type of cancer, does not appear to be commensurate in scope with the claimed invention since the claims broadly encompass a method of treating any and/or all hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies in any patient including humans. In the instant case, the Examiner recognizes that the specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. Specifically, the specification has not taught an appropriate tested dose for humans, the amount of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Thus, in view of the state of the art as described above, the specification appears to be silent on any of these critical aspects of gene therapy.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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